Background

• Currently, prostacyclin and its analogs are widely used in the clinical management of pulmonary arterial hypertension (PAH) and are generally considered the most effective targeted PAH therapy.1

• In PAH, the beneficial effects of prostacyclin in pulmonary arteries include vasodilation and inhibition of platelet aggregation/thrombosis, cell proliferation, and inflammation. These are thought to be mediated by binding to the prostacyclin (IP) receptor on smooth muscle cells and platelets. IP receptor binding triggers the activation of intracellular signaling resulting in increased intracellular cyclic adenosine monophosphate (cAMP).

• Ralinepag is an oral, potent and selective IP receptor agonist in development for pulmonary arterial hypertension (PAH).2,3

Objective

• The aim of the study was to compare the functional potency at the IP receptor (cAMP) with functional platelet and vascular effects of ralinepag with other non-prostanoid and prostacyclin mimetics (selipexag and iloprost) already licensed for PAH.

Methods

• Human IP receptor binding and selectivity was determined in recombinant IP, DP1, EP1, EP2, EP3, EP4, and TP receptor-expressing Chinese hamster ovary (CHO-K1) cells and normal human pulmonary artery smooth muscle cells (PASMCs).

• Functional potency assays, including cAMP accumulation and cell proliferation, were conducted in human PASMCs from patients with PAH. cAMP accumulation was also examined in recombinant CHO-K1 cells. Distal PASMCs were isolated from the lungs of patients with Group 1 PAH (idiopathic or associated with small cardiac defects). Human pulmonary arteries (PAs) were derived from histologically normal tissue of patients with cancer undergoing lobectomy.

• Distal PASMCs were mounted in a myograph and preconstricted with U46619 (thromboxane mimetic).

• The aim of the study was to compare the functional potency at the IP receptor (cAMP) with functional platelet and vascular effects of ralinepag in PAH patients grown in 9% serum and treated with agonists ± RO-1138452 for 96 hours.

Results

Ralinepag Binding Affinity and Selectivity

• Ralinepag had high binding affinity (Kd=3.4 nM) and selectivity at the human IP receptor (>2500-fold greater vs other prostanoid receptors) (Figure 1). Ralinepag has Favorable IP Receptor Activity

In Vitro

• Iloprost, ralinepag, and MRE-269 (selipexag metabolite) increased cAMP in IP receptor-expressing CHO cells (half-maximal effective concentration [EC50] 3.3, 24, and 151 nM, respectively), with similar potency in primary PASMCs (Figure 2).

• In PAs, ralinepag caused greater relaxation (EMax 98%) than iloprost.

• Ralinepag inhibited human adenosine diphosphate (ADP)-stimulated platelet aggregation versus MRE-269, a weak partial agonist (67% vs. 48%, respectively; Figure 3A).

• Ralinepag demonstrated greater functional potency compared with iloprost and MRE-269, providing a favorable vasorelaxant profile (EC50 449 nM vs 1579 nM) but similar in potency to iloprost (EC50 650 nM; Figure 3B).

• Ralinepag inhibited PASMC proliferation (half-maximal inhibitory concentration [IC50] 14 nM vs 155 nM, respectively; Figure 4A).

• The IP receptor antagonist RO-1138452 (1 μM) fully blocked cAMP production and cell proliferation by ralinepag and MRE-269, but only weakly inhibited or had varied effects on higher concentrations of iloprost (Figure 3B, 4B).

Conclusions

• Ralinepag is a potent IPRA with robust pharmacological responses in human platelets, PAs, and PASMCs.

• The IP receptor solely accounts for cAMP production and the antiproliferative effects of ralinepag and selipexag metabolite, but not iloprost.

• Ralinepag demonstrated greater functional potency and efficacy than the active selexipag metabolite, MRE-269, and a favorable vasorelaxant profile compared with iloprost and MRE-269, providing rationale for further investigation of ralinepag in PAH.

Disclosures

• John Adams: Empolyee of Arena Pharmaceuticals.

• Brendan Whittle: Consultant for Arena Pharmaceuticals.

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References


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